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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPELLANT :	HUNG, DAVID	ART UNIT :	1648
SERIAL NO. :	09/923,791	EXAMINER :	WINKLER, ULRIKE

FILED : AUGUST 8, 2001

TITLE : IDENTIFICATION OF VIRAL AGENTS IN BREAST DUCTS AND ANTIVIRAL THERAPY THEREFORE

January 13, 2006

Commissioner for Patents
Washington, DC 20231

APPEAL BRIEF

Sir:

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed November 10, 2005.

Real Party in Interest.

The real party in interest in this appeal is Cytyc Corporation, Inc., the assignee of the above-referenced patent application.

Related Appeals and Interferences.

There are no related appeals and/or interferences involving this application or its subject matter.

Status of Claims.

Claims 1, 2, 6-15, and 17-20 are the subject of this appeal. Claims 1, 2, 6-15, and 17-20 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Love et al. (USP 6,221,622) and Makita et al. (Breast Cancer Research, 1991), in view of Sukumar et al. (USP 5,763,415), King et al. (JNCI, 1983), Noguchi et al. (American Journal of Pathology, 1994), Gross G. (Intervirology, 1997), and Androphy (Ciba Found, Symposium, 1986). The claims appear in Appendix A. No other claims are pending. Claims 3-5, 16, and 21-22 have been cancelled.

Status of Amendments.

All of Appellant's amendments have been entered.

Summary of the Claimed Subject Matter.

The pending claims of the present invention are directed to a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer by introducing a ductal access tool into a breast duct, the access tool comprising a single elongated lumen for introducing fluid into the breast duct through the elongated lumen; retrieving a ductal fluid sample from within the breast duct through the same elongated single lumen of the access tool, where the ductal fluid is free of any ductal fluid from another duct of the breast, and detecting a viral agent in the ductal fluid sample. If a viral agent is detected, an antiviral agent specific for the detected viral agent may be administered to the patient either intraductally or systemically.

Grounds of Rejection to be Reviewed on Appeal.

Whether claims 1, 2, 6-15, and 17-20 are patentable under 35 U.S.C. § 103(a) over Love

et al. (USP 6,221,622) and Makita *et al.* (Breast Cancer Research, 1991), in view of Sukumar *et al.* (USP 5,763,415), King *et al.* (JNCI, 1983), Noguchi *et al.* (American Journal of Pathology, 1994), Gross G. (Intervirology, 1997), and Androphy (Ciba Found, Symposium, 1986).

ARGUMENT

Issue- Whether claims 1, 2, 6-15, and 17-20 are patentable under 35 U.S.C. 103(a), over Love et al. (USP 6,221,622) and Makita et al. (Breast Cancer Research, 1991), in view of Sukumar et al. (USP 5,763,415), King et al. (JNCI, 1983), Noguchi et al. (American Journal of Pathology, 1994), Gross G. (Intervirology, 1997), and Androphy (Ciba Found, Symposium, 1986).

The Examiner has rejected Appellant's claims 1, 2, 6-15, 17-20 under 35 U.S.C. 103(a) as being unpatentable over Love et al. (USP 6,221,622) and Makita et al. (Breast Cancer Research, 1991), in view of Sukumar et al. (USP 5,763,415), King et al. (JNCI, 1983), Noguchi et al. (American Journal of Pathology, 1994), Gross G. (Intervirology, 1997), and Androphy (Ciba Found, Symposium, 1986).

The original rejection of claims 1, 2, 6-15, 17-20 under 35 U.S.C. 103(a) was made in the first Office Action of December 28, 2004. In the December 24, 2004 Office Action, the Examiner stated that "[o]ne having ordinary skill in the art would have been motivated to use the fluid treatment system of Love *et al.* which introduces a washing fluid into the breast duct and apply it to the fluid retrieval and analysis taught in Makita *et al.*, King *et al.*, and Noguchi *et al.*, each establish that the presence of papillomavirus in the epithelial layers of the breast duct was known in the art." (see pages 7, lines 10-14). The Examiner also pointed out that "[s]ukamar et

al. teaches the introduction of a composition into the breast duct, which destroys the epithelial tissue a primary site for papillomavirus infection. Androphy and Gross teach the use of interferon for the treatment of papillomavirus, the interferon can be administered directly to the papillomavirus lesion or it can be administered systemically." (see page 7, lines 17-21). The Examiner then goes on the state that "...taken what was know in the prior art as a whole, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, to identify the presence of papillomavirus in a single breast duct and apply treatment to the single breast duct." (see page 7, line 22 to page 8, line 2). The Appellant respectfully disagrees that the Examiner has established a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

I. The prior art references (or references when combined) are not enabled and do not teach or suggest all the claim limitations.

To establish a *prima facie* case of obviousness includes the criteria that all of the

limitations of the claims must be taught or suggested by the prior art. *In re Royka* 490 F.2d 981 (C.C.P.A. 1974). Since, under the obviousness standard, the prior art must teach or suggest all the limitations of the claims, then it is axiomatic that non-enabling disclosures should not be considered prior art (See *e.g.*, *In re* Wilder, 429 F.2d 447, 166 USPQ 545, 548 (C.C.P.A. 1970).

A. Love et al. (USP 6,221,622)

In the Office Action of December 28, 2004, the Examiner stated that the Love *et al.* (USP 6,221,622) (hereinafter Love) teaches "...the ability to irrigate (introduce fluid) and wash (remove fluid) from a single breast duct and using the material for the analysis of precursor cancer markers. The reference teaches that ducts may be washed multiple times. In addition, the reference suggests that treatment can be targeted to an effected duct (column 1, line 53-56). The reference does not specifically teach detecting a viral agent, the reference uses terms such as cancer or pre-cancer conditions. This broad category encompasses viral agents, which are known to be involved in the cancer pathology." (see page 3, last sentence to page 4, first paragraph).

The Appellant respectfully disagrees that Love teaches or suggests a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer, by introducing a ductal access tool, comprising a single elongated lumen, into the breast duct, introducing wash fluid through the single elongated lumen into a breast duct; retrieving the ductal wash fluid sample from within the breast duct through the same elongated single lumen of the ductal access tool, where the ductal wash fluid is free of any ductal fluid from another duct of the breast; and detecting a viral agent in the ductal wash fluid sample.

Even though the Examiner admits that Love teaches a dual lumen catheter (see December 28, 2004 Office Action, page 3, lines 15-17), the Examiner further added that "[t]he Love reference still applies even if the claims were limited to a single lumen catheter because the reference teaches the use of a syringe to wash the breast duct." (see December 28, 2004 Office Action, page 4, lines 16-18). The Appellant respectfully disagrees. Love only mentions the use of a syringe to wash a breast duct through the lumen of a dual-lumen catheter. Nowhere in Love is there a description of a single lumen catheter being used as the primary device to irrigate and remove fluid from a single breast duct. The Examiner argued that the Love reference "...teaches that the Love and Barsky prior art reference uses a single lumen catheter and that the prior art reference contemplated the double lumen catheter but did not actually use such a catheter in the reference." (see June 16, 2005 Office Action, page 3, lines 18-20). The Examiner argued further that "[t]he purpose of the Love patent was to improve over the prior art by using a double lumen catheter indicating that the prior art *only* included the single elongated lumen catheter." (emphasis added) (see June 16, 2005 Office Action, page 3, lines 20-22).

The statement that the Love and Barsky reference teaches the use of a single lumen catheter because the double lumen catheter, specifically taught in Love, is a necessary improvement over Love and Barsky, is mere speculation put forth by the Examiner. To establish a *prima facie* case of obviousness includes the criteria that all of the limitations of the claims must be taught or suggested by the prior art cited by the Examiner. The Examiner has not cited the Love and Barsky reference against the claims of the present invention, nor has the Examiner proffered any proof that Love and Barsky teaches or suggests a single lumen catheter. In

response, the Examiner stated that "...a reference is valid for all that it teaches..." and thus "...the '622 patent teaches the following:

> Prior attempts to obtain cellular material from individual breast ducts have been only partly successful. As reported by the inventor herein, in Love and Barsky (1996) The Lancet 348:997-999, breast ducts have been cannulated with a rigid cannula and instilled with very small volumes (0.2ml to 0.5 ml) of saline. Saline was recovered separately through a capillary tube, and cellular material recovered from the saline. It was not clear, however, if cellular material was recovered from most or all portions of the ductal network. Unless such representative samples can be obtained, reliable diagnostics cannot be performed. <u>While the paper proposes development of a two-lumen catheter, no such catheter or its use is described in the publication</u> (see '622, column 2, lines 8-20).

Thus the prior art referred to in the '622 patent only used a single lumen catheter." (see October 18, 2005 Office Action; page 2, last paragraph to page 3, first paragraph). The Appellant respectfully disagrees.

Although the Appellant agrees that a reference is valid for all that it teaches, the Appellant disagrees that Love or any prior art referred to in Love teaches or suggests a single lumen catheter that is capable of instilling and withdrawing fluid into a breast duct through the same single lumen. The Examiner appears to be arguing that, although Love only claims a dual lumen catheter, by distinguishing itself from the prior art Love <u>teaches</u> a single lumen catheter by making reference to Love and Barsky. This is nonsensical. First, just because Love teaches a catheter with two lumens does not necessarily mean that the Love and Barsky reference teaches a catheter with only one lumen. The description of the research done in Love and Barsky

mentioned in Love only makes reference to breast ducts that "...have been cannulated with a rigid cannula and instilled with very small volumes (0.2ml to 0.5ml) of saline." The Appellant would argue that such a statement is not definitive as to the presence or absence of a single lumen within the cannula. Second, even assuming that Love and Barsky teaches a single lumen catheter, Love teaches away from using such a catheter. The preferred embodiment of the device of Love is a double lumen catheter which was developed because of previous problems of obtaining cellular material with the device described in Love and Barsky.

Even assuming *arguendo* that Love teaches or suggests the use of a single lumen catheter, it is not an enabling disclosure because it does not teach or suggest a single lumen catheter that is capable of instilling fluid into a breast duct and withdrawing the fluid through the same single lumen. Love teaches a dual lumen catheter for the injection and withdrawal of fluid from a breast duct. The Love and Barsky reference contained within Love uses two separate devices to irrigate and withdraw fluid from a breast duct ("Saline was recovered separately through a capillary tube"; see Love column 2; lines 13-14). Therefore, neither Love nor the incorporated Love and Barsky reference teach or suggest a single lumen catheter for the introduction and removal of fluid from a breast duct via the same single lumen.

Thus, the Examiner has not established a *prima facie* case of obviousness because Love does not teach or suggest, either alone or in combination, a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer, by introducing a ductal access tool, comprising a single elongated lumen, into the breast duct; introducing wash fluid through the single elongated lumen into a breast duct; and retrieving the ductal wash fluid sample from

within the breast duct through the same elongated single lumen of the ductal access tool.

B. Makita *et al.* (Breast Cancer Research, 1991)

In the Office Action of December 28, 2004, the Examiner stated that the Makita *et al.* (Breast Cancer Research, 1991) reference (hereinafter Makita) establishes that "...it was known in the art that papillomavirus is present in the epithelial cells of the breast." (see page 5, lines 14-15. The Appellant disagrees. Makita teaches the use of duct endoscopy and endoscopic biopsy in the evaluation of nipple discharge. Nowhere in Makita is there mention of the papilloma virus being found in the epithelial cells of the breast. Makita describes histological diagnosis of tissues obtained from mastectomies as having ductal papillomas (see *e.g.*, Table 2), however, papillomas are defined as small, benign tumors that grow within a milk duct of the breast. Papillomas are not a cancer and very unlikely to develop into a cancerous mass. There is no mention in Makita of the detection or treatment of the papilloma virus and there is no suggestion that the papilloma virus can be found in epithelial cells of the breast. Thus, Makita simply does not teach or suggest that papillomavirus is present in the epithelial cells of the breast.

The Appellant has also argued that Makita does not make up for the deficiency of Love, *i.e.* that there is no teaching or suggestion in Love or any of the cited references of the use of a single lumen catheter to wash and collect fluid from a single breast duct (see response to December 28, 2004 Office Action filed March 24, 2005; page 8, second paragraph). The Examiner disagreed, stating that Makita "...teaches the aspiration of ductal fluid/sample using an outer cylinder, the 'outer' cylinder when aspirating the sample is a single elongated lumen present in the breast duct." (see June 13, 2005 Office Action page 4 first full paragraph). The

Applicant respectfully disagrees with the Examiner's characterization of Makita *et al.* Makita *et al.* does not teach the aspiration of ductal fluid. Makita *et al.* teaches obtaining a biopsy of tissue with an endoscope. Thus, Makita *et al.* cannot be used to teach the use of a single lumen catheter to wash and collect fluid from a single breast duct. An endoscope is not a device capable of injecting and then retrieving fluid from a breast duct. In response to the Appellant's arguments, the Examiner maintained the assertion that Makita teaches the removal of fluid from a breast duct because Makita mentions that "...after confirming that the lesion is inside the outer cylinder, we take out the endoscope and aspirate through the outer cylinder using an inserted syringe, so we can get the lesion, as a small bit of tissue or fluid sample, inside the outer cylinder. (see Makita *et al.* page 181, column 1, first paragraph)." (see October 18, 2005 Office Action; page 5, lines 15-17). The Appellant would argue that the primary purpose of Makita is to teach the removal of tissue via ductal endoscopy. The fact that some fluid may be aspirated into the ductoscope at the same time the tissue sample is being collected is merely incidental to the primary purpose of an endoscopic biopsy. Thus, one of skill in the art at the time the invention was made would not look to Makita as teaching how to remove fluid from a breast duct.

Thus, the Examiner has not established a *prima facie* case of obviousness because Makita does not teach or suggest, either alone or in combination with any other cited reference, a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer, by introducing a ductal access tool, comprising a single elongated lumen, into the breast duct; introducing wash fluid through the single elongated lumen into a breast duct; and retrieving the ductal wash fluid sample from within the breast duct through the same elongated single lumen of

the ductal access tool.

C. Sukumar et al. (USP 5,763,415)

In the Office Action of December 28, 2004, the Examiner stated that Sukumar *et al.* (USP 5,763,415) (hereinafter Sukumar) establishes that "...it was know in the art to introduce a treatment agent into the breast duct." (see page 6, lines 2-3). The Examiner admits that Sukumar does not teach using a viral specific agent, however, the Examiner attempts to suggest that such an agent is somehow related to the destruction of viruses because the agent"...destroys epithelial cells, which are cells that are infected by papillomavirus." (see December 28, 2004 Office Action page 5, last paragraph). The Appellant agrees that Sukumar teaches the use of agents that destroy epithelial cells, however, the Appellant would argue against any assertion that the agents are in any way connected to the detection or eradication of the papilloma virus. There is simply no mention anywhere in Sukumar of the detection or treatment of the papilloma virus in the epithelial cells of the breast. Thus, the Appellant would argue that Sukumar is not an enabling disclosure for the diagnosis or the treatment of papilloma virus in a breast duct.

D. King et al. (JNCI, 1983)

In the Office Action of December 28, 2004, the Examiner stated that King *et al.* (JNCI, 1983) (hereinafter King) teaches that "...fluid obtained from nipple aspirate can be used to assess the presence of a viral agent, papilloma and papilomatosis (see Table 5). The reference obtains fluid from multiple ducts and not a single duct. The reference establishes that at the time the

invention was made, it was known in the art that papillomavirus can be detected in fluid samples obtained from breast ducts." (see page 6, lines 4-5). The Appellant respectfully disagrees.

King examined the association between nipple aspirate fluid (NAF) cytology and the presence of atypical proliferative disease (APD) of breast ducts. There is no reference to the papillomavirus.

As mentioned in the Appellant's response of March 24, 2005, Table 5 of King describes histologic types of breast disease tissues, not breast fluid or cells from breast fluid (see page 2, column 1, lines 3-10). The histological types described in table 5 come from tissues subsequently collected from biopsies or mastectomies, not from the washing of the breast ducts. Thus, King fails to teach the detection a viral agent in a ductal fluid sample. The Examiner subsequently argued that "...the instant invention uses terms comprising which does not limit the detection of the viral agent to only fluid because it can have additional elements present. The ordinary artisan would know that any fluid removed from a breast duct would contain not only liquid but also cells." (see June 15, 2005 Office Action page 4, lines 10-13). The Appellant disagrees.

The Appellant would argue that the Examiner's attempt to find equivalence with the examination of cells in a liquid specimen to the examination of tissue specimens from a biopsy is misplaced. King describes the collection of NAF and the subsequent examination and classification of epithelial cells contained in the NAF (see page 1, column 1, lines 31-36). There is no description in King of the detection of a viral agent in ductal fluid. The histological types

described in table 5 come from tissues subsequently collected from biopsies or mastectomies, not from the washing of the breast ducts.

Thus, King simply does not teach or suggest that papillomavirus can be detected in fluid samples obtained from breast ducts.

The Examiner then proceeded to argue that, even if there is no support in King for the examination of the papillomavirus in ductal fluid, King is still relevant as prior art because "...the instant specification does not limit ductal fluid to the liquid portion." (see June 15, 2005 Office Action page 4, lines 13-14). The Examiner seems to be arguing that because ductal fluid contains epithelial cells, and the King reference teaches the examination of epithelial cells which are the target of the papilloma virus, therefore, the King reference would also teach the examination of cells in ductal fluid to assess the presence of a viral agent. This clearly is improper. The Appellant would argue that the claims and specification of Appellant's application are quite clear. Although Appellant does not argue that cells and other biological material can be found in ductal fluid, it is axiomatic that a "ductal fluid" specimen would be comprised mainly of a liquid. The Examiner's attempt to equate the examination of ductal fluid and its contents, particularly viral agents, with the examination of tissues obtained by biopsies or mastectomies for pathological changes, should fail. More importantly, there is simply no mention anywhere in King of the detection or treatment of the papilloma virus in the epithelial cells of the breast, let alone any fluid that may be found in a breast duct. Thus, the Appellant would argue that King is not an enabling disclosure for the detection of papilloma virus in a breast duct.

Thus, the Examiner has not established a *prima facie* case of obviousness because King does not teach or suggest, either alone or in combination, that the papillomavirus can be detected in fluid samples obtained from breast ducts.

E. Noguchi et al. (American Journal of Pathology, 1994)

In the Office Action of June 1, 2004, the Examiner stated that the Noguchi *et al.* (American Journal of Pathology, 1994) (hereinafter Noguchi) teaches using PCR analysis to determine the presence of papillomavirus in the breast duct. The Appellant disagrees. Noguchi performs clonal analysis of intraductal papillomas by the PCR amplification of the PGK gene. The PGK gene is a human gene found on the X chromosome. Nowhere in Noguchi is there any mention of the detection of papilloma virus in a breast duct.

Thus, the Examiner has not established a *prima facie* case of obviousness because Noguchi does not teach or suggest, either alone or in combination, that the papillomavirus can be detected in fluid samples obtained from breast ducts.

F. Gross G. (Intervirology, 1997) and Androphy (Ciba Found, Symposium, 1986)

In the Office Action of June 1, 2004, the Examiner stated that both Gross G. (Intervirology, 1997) and Androphy (Ciba Found, Symposium, 1986) (hereinafter Gross and Androphy respectively), established that it was known in the art at the time the invention was made to treat papillomavirus infection with an antiviral agent. The Appellant does not disagree that, at the time the invention was made, there were know antiviral agents that have been used to

treat viral infections. However, the Appellant does not agree that any of the agents mentioned in Gross or Androphy are specific for the papilloma virus, nor are they specific for the Epstein-barr virus, or the herpes virus. Also, the Appellant would point out that there is no mention, either in Gross or Androphy, of the application of an anti-viral agent into a breast duct for the treatment of a viral infection. There is also no mention in Gross or Androphy of the papilloma virus or any other virus being found in breast tumors, lesions, cells, or ductal fluid.

Conclusion

To establish a *prima facie* case of obviousness includes the criteria that all of the limitations of the claims must be taught or suggested by the prior art. The pending claims of the present invention are directed to a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer by introducing a ductal access tool into a breast duct, the access tool comprising a single elongated lumen for introducing fluid into the breast duct through the elongated lumen, retrieving a ductal fluid sample from within the breast duct through the same elongated single lumen of the access tool, where the ductal fluid is free of any ductal fluid from another duct of the breast, and detecting a viral agent in the ductal fluid sample. If a viral agent is detected, an antiviral agent specific for the detected viral agent may be administered to the patient either intraductally or systemically. The Examiner has argued that the prior art established that "...it was known to introduce/extract washing fluids using a microcatheter. The prior art established that it was known to introduce therapeutic agents into the breast directly. It was also known in the prior art that papillomavirus lesion were found in the breast duct. Based

on what was know in the prior art at the time the invention was made, it would have been obvious to one of ordinary skill in the art to (1) utilize a duct washing system for the diagnosis of the presence of a viral agent in the breast duct and (2) utilize a duct washing system for the diagnosis of the presence of a viral agent followed by the introduction of an antiviral agent to the patient." (see December 28, 2004 Office Action page 7, lines 4-10). The Appellant disagrees.

The Appellant has demonstrated above that, although it may have been known to separately introduce and remove fluid from a breast duct, there was no teaching in the art about the introduction of fluid into a breast duct using a single lumen catheter and the removal of the fluid through the same single lumen catheter as taught by the method of the present invention. The Examiner states that it was known to introduce therapeutic agents directly into the breast; however, as demonstrated above, the prior does not teach or suggest a method to introduce an antiviral agent into a breast duct as taught by the method of the present invention. The Examiner also states that it was also known in the prior art that papillomavirus lesion were found in the breast duct. The Appellant disagrees that any of the references cited by the Examiner clearly demonstrates that papilloma lesions can be found in breast ducts. Even assuming *arguendo*, that the prior art teaches or suggests that there are papilloma lesions within a breast duct, the Appellant would argue that there is nothing in the prior art to teach or suggest the presence of a viral agent in the fluid of a breast duct.

Thus, the Examiner has not established a *prima facie* case of obviousness because Love, Makita, Sukumar, King, Noguchi, Gross, or Androphy does not teach or suggest, either alone or in combination, all of the limitations of the present invention which claims a method for

identifying or treating a patient at risk for or having a breast precancer or breast cancer, by introducing a ductal access tool, comprising a single elongated lumen, into the breast duct, introducing wash fluid through the single elongated lumen into a breast duct; retrieving the ductal wash fluid sample from within the breast duct through the same elongated single lumen of the ductal access tool, where the ductal wash fluid is free of any ductal fluid from another duct of the breast; and detecting a viral agent in the ductal wash fluid sample.

For these reasons, the rejection of claims 1, 2, 6-15, and 17-20 under U.S.C. § 103(a), should be reversed.

II. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention. See, *e.g.*, *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

A new combination of elements can be patented "whether it be composed of elements all new, partly new or all old." *Rosmount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546, 221 USPQ 1, 7 (CAFC 1984). The Court of Appeals for the Federal Circuit has forcefully stated

that a claim rejection must provide a specific motivation in the art for combining elements from cited art in order to establish obviousness of a new combination.

> "[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999), emphasis added.

Dembiczak involved patent claims to "a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with trash or leaves, to resemble a Halloween-style pumpkin, or jack-o'-lantern." *Dembiczak*, 996, 1616. The prior art cited by the Board included: a book describing how to teach children to make a "Crepe Paper Jack-O-Lantern;" a book describing a method of making a "paper bag pumpkin" by stuffing a bag with newspapers, painting it orange, and then painting on facial features with black paint; a U.S. Patent describing a bag apparatus wherein the bag closure is accomplished by the use of folds or gussets in the bag material; design patents issued to Dembiczak; and prior art "conventional" plastic lawn or trash bags. The Federal Circuit held that the claimed pumpkin-style trash bag was not obvious because there was no clear, particular motivation to combine the cited references.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

> In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).
>
> ... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements."). *Ruiz* at 1167

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. The motivation cited in the Office Action for the proposed combination is as follows:

> "...one having ordinary skill in the art would have been motivated to use the fluid retrieval system of Love et al., which introduces a washing fluid into the breast duct and apply it the fluid retrieval and analysis taught in Makita et al. King et al., and Noguchi et al., each establish that the presence of papillomavirus in the epithelial layers of the breast duct was known in the art." "...Sukumar et al., teach the introduction of a composition into the breast duct, which destroys the epithelial tissue a primary site for papilloma infection. Androphy and Gross teach the use of interferon for the treatment of papillomavirus, the interferon can be administered directly to the papillomavirus lesion or it can be administered systemically."

(see December 28, 2004 Office Action; page 7, line 10-21).

This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required. The Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to use a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer, by introducing a ductal access tool, comprising a single elongated lumen, into the breast duct, introducing wash fluid through the single elongated lumen into a breast duct; retrieving the ductal wash fluid sample from within the breast duct through the same elongated single lumen of

the ductal access tool, where the ductal wash fluid is free of any ductal fluid from another duct of the breast; and detecting a viral agent in the ductal wash fluid sample.

Love *et al.* does not teach or suggest the use of a single lumen catheter to introduce and remove fluid from a breast duct. The deficiency of Love *et al.* cannot be made up by Makita *et al.*, Sukumar *et al.*, King *et al.*, Noguchi *et al.*, Gross G., or Androphy. There is simply no teaching in any of the cited references of the use of a single lumen catheter to wash and collect fluid from a single breast duct. Additionally, it would not have been obvious to one of ordinary skill in the art to modify the dual lumen catheter of Love *et al.* so that it irrigate and retrieve a ductal sample because no motivation exists for such a modification and such a modification is contrary to the common knowledge of the ordinary artisan.

Makita *et al.* does not teach or suggest a method for fluid retrieval from a breast duct. As mentioned previously, Makita *et al.* teaches the use of ductal endoscopy for the retrieval of tissue biopsies from ductal lesions. Ductal endoscopy is not a methodology that is conducive to the retrieval of small amounts of fluid from a breast duct. A passing mention in Makita *et al.* that some fluid may be obtained in the process of collecting a tissue specimen from a breast lesion should not render the reference enabled for teaching a method for specifically removing fluid from a breast duct for analysis. Even assuming *arguendo*, that Makita *et al.* is an enabling disclosure for teaching the removal of fluid from a breast duct, the Examiner has failed to provide evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings of Makita *et al.* with Love *et al.* Love *et al.* teaches ductal lavage which is a non-invasive procedure for the collection of small amounts of fluid injected into the breast

ducts of patients and to examine the collected fluid for the presence of markers (e.g., viral agents, abnormal cells, proteins, nucleic acids, etc.) which would indicate the presence of a precancerous or cancerous lesion. Makita *et al.* teaches ductal endoscopy which is a procedure for the visualization of a breast lesion through an endoscope and the subsequent biopsy of the lesion through the same instrument. The obviousness rejection is based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention.

The Examiner argues that King *et al.* and Noguchi *et al.* each establish that the presence of papillomavirus in the epithelial layers of the breast duct was known in the art. The Appellant has clearly demonstrated that neither King *et al.* nor Noguchi *et al.* teach or suggest the presence or absence of the papilloma virus in breast epithelial tissues, cells, or fluids. Even assuming *arguendo*, that King *et al.* and Noguchi *et al.* teach the presence of the papillomavirus in the epithelial layers of the breast duct, the Examiner has failed to provide evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings of King *et al.* and Noguchi *et al* with Love *et al.* and Makita *et al.* King *et al.* teaches the examination of fluid obtained via nipple aspiration which is a completely different procedure than ductal lavage and Noguchi *et al.* examines gene expression from samples obtained via surgical excision. The obviousness rejection is based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention.

The Examiner also argues that Sukumar *et al.* teaches the introduction of a composition

into the breast duct, which destroys the epithelial tissue a primary site for papilloma infection. The Appellant has clearly demonstrated that Sukumar *et al.* does not teach or suggest the presence or absence of the papilloma virus in breast epithelial tissues, cells, or fluids. Even assuming *arguendo*, that Sukumar *et al.* teaches the presence of the papillomavirus in the epithelial layers of the breast duct, the Examiner has failed to provide evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings of Sukumar *et al.* with Love *et al.* and Makita *et al.* Sukumar teaches the non-specific eradication of epithelial cells within a breast duct. There is nothing in the teachings of Love *et al.* and Makita *et al.* that would suggest the application of a therapeutic into a breast duct. The obviousness rejection is based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention.

The Examiner also argues that Androphy and Gross teach the use of interferon for the treatment of papillomavirus and that interferon can be administered directly to the papillomavirus lesion or it can be administered systemically. The Examiner has failed to provide evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings of Androphy and Gross with Love *et al.* and Makita *et al.* The teachings of Androphy and Gross do not mention the administration of antiviral agents to a breast duct. Since neither Love *et al.*, Makita *et al.*, Sukumar *et al.*, King *et al.* or Noguchi *et al.* teach or suggest the presence or absence of the papilloma virus in a breast duct, one of skill in the art would not have been motivated to combine these references. The obviousness rejection is based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular

motivation in the references to reach the claimed invention.

Lastly, the Examiner argues that it would have been obvious to one skilled in the art to utilize a duct washing system for the diagnosis of the presence of a viral agent in the breast duct followed by the introduction of an antiviral agent to the patient. The Appellant disagrees. The Federal Court has consistently emphasized that Section 103 requires that the invention be evaluated as a "whole" (see *e.g.*, Kimberly-Clarke Corp vs. Johnson & Johnson, 745 F. 2d 1437, 223 USPQ 603, 609-610 (Fed Cir. 1984)). In the case at hand, the Examiner has presented disparate references to provide random elements of the claims. The Examiner has failed to cite any references that teach or suggest, either alone or in combination, a method for identifying or treating a patient at risk for or having a breast precancer or breast cancer, by introducing a ductal access tool, comprising a single elongated lumen, into the breast duct, introducing wash fluid through the single elongated lumen into a breast duct; retrieving the ductal wash fluid sample from within the breast duct through the same elongated single lumen of the ductal access tool, where the ductal wash fluid is free of any ductal fluid from another duct of the breast; and detecting a viral agent in the ductal wash fluid sample as a whole.

Thus, a *prima facie* case of obviousness has not been established because the Examiner has not presented evidence that one having ordinary skill in the art would have been motivated to combine Love *et al.*, Makita *et al.*, Sukumar *et al.*, King *et al.*, Noguchi *et al.*, Gross G., or Androphy to make the claimed invention. In view of the foregoing, the rejection of claims 1, 2, 6-15, and 17-20 under U.S.C. § 103(a), should be reversed.

CONCLUSION

In view of the arguments presented above, the Appellant contend that each of claims 1, 2, 6-15, and 17-20 are patentable. Therefore, reversal of the rejection under 35 U.S.C. §103(a) is respectfully solicited.

Respectfully ~~submitted~~,

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APPENDIX A: PENDING CLAIMS

1. A method for identifying a patient having an increased risk for developing breast precancer or breast cancer, said method comprising the following steps:

(a) introducing a ductal access tool into a breast duct, said access tool comprising a single elongated lumen;

(b) introducing a fluid into the breast duct through said elongated lumen;

(c) retrieving a ductal fluid sample from within the breast duct through said lumen, said ductal fluid being free of any ductal fluid from another duct of the breast; and

(d) detecting a viral agent in the ductal fluid sample.

2. A method as in claim 1, wherein the viral agent is selected from the group consisting of a whole virus, a portion of a virus, a viral protein, a viral nucleic acid, and a viral marker, in the sample.

6. A method as in claim 1, wherein, steps (a)–(d) of the method are repeated for a plurality of breast ducts.

7. A method as in claim 1, further comprising analyzing the ductal fluid for

abnormal cytology.

8. A method as in claim 1, wherein a viral agent is detected, and further comprising the steps of: periodically repeating steps (a)-(c); and monitoring a variable selected from the group consisting of a viral titer, concentration of a viral agent, and presence of a viral marker in the ductal fluid samples.

9. A method as in claim 8, wherein the viral agent is monitored and the viral agent is selected from the group consisting of a whole virus, a portion of a virus, a viral protein, a viral nucleic acid, and a viral marker by taking repeated periodic ductal fluid samplings.

10. A method as in claim 8, wherein the periodicity is selected from the group consisting of daily, weekly, biweekly, monthly, bimonthly, every six months, annually, and biannually.

11. A method as in claim 1, wherein the viral agent is selected from the group consisting of papilloma virus, Epstein-barr virus, and herpes virus.

12. A method of treating a patient at risk for or having a breast precancer or breast cancer, said method comprising the following steps:

(a) introducing a ductal access tool into a breast duct, said access tool comprising a single elongated lumen;

(b) introducing a fluid into the breast duct through said elongated lumen;

(c) retrieving a ductal fluid sample from within the breast duct through said lumen;

(d) detecting a viral agent in the retrieved ductal fluid sample from the breast duct; and

(e) delivering to the patient a composition comprising an antiviral agent specific for the detected viral agent.

13. A method as in claim 12, wherein the viral agent is selected from the group consisting of a whole virus, a portion of a virus, a viral protein, a viral nucleic acid, and a viral marker.

14. A method as in claim 12, wherein the antiviral agent is delivered intraductally to the breast duct in which the viral agent has been detected.

15. A method as in claim 12, further comprising repeating steps (a)-(c) for a plurality of additional breast ducts; and wherein a viral agent is detected in at least one of the fluid samples separately retrieved from the plurality of additional breast ducts.

17. A method as in claim 12, wherein the viral agent is selected from the group

consisting of papilloma virus, Epstein-barr virus, and herpes virus.

18. A method as in claim 12, wherein the antiviral agent is selected from the group consisting of an anti-HPV viral agent, and anti-EBV viral agent, and an anti-herpes viral agent.

19. A method as in claim 12, wherein said delivering step includes delivering the composition comprising said antiviral agent systemically.

20. A method as in claim 14, wherein analyzing comprises measuring a quality of the ductal fluid or ductal cells *in situ*.

APPENDIX B: EVIDENCE

NONE

APPENDIX C: RELATED PROCEEDINGS

NONE

TRANSMITTAL OF APPEAL BRIEF (Large Entity)

Docket No. 12.019011

In Re Application Of: **David Hung**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/923,791	08/08/01	Winkler, Ulrike	0000 38732	1648	9920

Invention: **IDENTIFICATION OF VIRAL AGENTS IN BREAST DUCTS AND ANTIVIRAL THERAPY THEREOF**

COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on **November 10, 2005**

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Dated: 1/13/2006

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Application No. **09/923,791**	Filing Date **August 8, 2001**	Examiner **U. Winkler**	Customer No. **0000 38732**	Group Art Unit **1648**

Invention: **IDENTIFICATION OF VIRAL AGENTS IN BREAST DUCTS AND ANTIVIRAL THERAPY THEREOF**

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